PTO/SB/33 (07-05)

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional)
026549-000100US

I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on February 8, 2008.

TOWNSEND and TOWNSEND and CREW LLP

By: Jo Ann Dallara

Typed or printed name Jo Ann Honcik Dallara

Application Number	Filed
10/009,809	April 26, 2002

First Named Inventor
Eisenberg, Ronit Sagi

Art Unit	Examiner
1644	Crowder, Chun

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed.
(Form PTO/SB/96)

☒ attorney or agent of record.
Registration number 31,677.

☐ attorney or agent acting under 37 CFR 1.34.

Registration number if acting under 37 CFR 1.34. _____

Kenneth A. Weber
Signature

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Telephone number

February 8, 2008
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required.
Submit multiple forms if more than one signature is required, see below*.

☒ *Total of 1 forms are submitted.

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TOWNSEND and TOWNSEND and CREW LLP

By: Jo Ann Dallara
Jo Ann Honcik Dallara

PATENT
Docket No.: 026549-000100US
Client Ref. No.: 30836
Customer No. 20350

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 1519
Ronit Eisenberg et al.	Examiner: Crowder, Chun
Application No.: 10/009,809	Art Unit: 1644
Filed: April 26, 2002	
For: CELL PENETRATING ANTI-ALLERGIC PEPTIDES	PRE-APPEAL BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicants request review prior to filing their Appeal Brief. The Request for review is being co-filed with a Notice of Appeal. The outstanding rejection is appropriate for a pre-appeal conference. The rejection reflects a misunderstanding of how surprising results can traverse a *prima facie* case of obviousness. Here the applicants present evidence of four seemingly equivalent combinations—but only one works. The other three combinations failed.

THE INVENTION:

This invention provides for an anti-allergy agent comprising a cell penetrating peptide [CPP] from Kaposi fibroblast growth factor fused to either of two specific inhibitors of mast cell activation, $G\alpha t$ or $G\alpha i_3$. In a test of four different CPPs, the claimed CPP from Kaposi fibroblast growth factor [Seq ID No. 3] was surprisingly

discovered to be the *only* CPP able to transport its inhibitor domains in a manner that **inhibited** mast cell activation.

Independent claim 63 is illustrative:

> 74. A method of inhibiting mast cell degranulation in a subject, the method comprising administering to the subject a pharmaceutically effective amount of a therapeutic agent, wherein said therapeutic agent comprises a complex molecule which comprises a peptide having a first segment having an amino acid sequence AAVALLPAVLLALLAP (SEQ ID NO:3) and a second segment having an amino acid sequence KENLKDCGLF (SEQ ID NO:2) or KNNLKECGLY (SEQ ID NO:1), said first segment being joined to said second segment through a linker, thereby inhibiting mast cell degranulation in the subject.

TECHNICAL OVERVIEW:

This invention provides for a novel anti-allergy agent. The agent works by inhibiting the release of histamines by mast cells. Mast cell secretion are at the heart of many serious allergies.

The claimed agents are a fusion of a cell penetrating peptide [CPP] with one of two different mast cell inhibitors. Cell penetrating peptides are a known class of peptides that can transport themselves across a cell membrane into the cytosol of a cell. The prior art teaches that CPPs can be fused to biologically active proteins and will facilitate their delivery into cells.

In the subject invention, the two mast cell inhibitors are in the prior art. They are designated $G\alpha i_3$ and $G\alpha t$ (see Lin *et al.*, at endnote 30) and are 9 and 10 amino acids long, respectively.

While cell penetrating peptides are known, the technology is not well understood. Both Examiners Nolan and Crowder acknowledged the field as unpredictable. Examiner Nolan wrote in the non-final Office Action of April 8, 2005, on page 4:

> Claims 44, 52-62 [are -sic] rejected under 35 U.S.C. §112, first paragraph, because the specification while being enabling for using the importation peptide AAVALLPAVLLALLAP, does not reasonably provide enablement for the use of any importation molecule to treat allergies. … Since applicant's working examples demonstrate unpredictability in the ability of the import peptide to successfully transfer the inhibitory degranulation peptide to mast cells in vitro it would require an undue amount experimentation to practice the full scope of the claimed invention in vivo.

Examiner Crowder wrote on page 4 of the non-final Office Action mailed August 2, 2006:

> Claims 63-70, 72-74 and 77-80 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement … The state of the art recognizes that the effect of cell-penetrating peptides can be unpredictable due to limited knowledge of the mechanisms associated with mast cell exocytosis.

The §103 Rejection and Response:

The Examiner has maintained her rejection of the pending claims as obvious over Holgate in view of Aridor and Lin. Holgate is relied upon as generally teaching that pharmacological agents can inhibit mast cell degranulation and these agents are useful for treating diseases such as asthma. Aridor teaches Seq. No. 1 (KNNLKECGLY) and Seq. No. 2 (KENLKDCGLF). Lin teaches the Kaposi CPP (AAVALLPAVLLALLAP).

The Examiner presents the *prima facie* case of obviousness by arguing that she has identified the salient elements of the claims, a motivation to combine the elements, and a reasonable expectation that once combined, the recited elements would function to inhibit histamine release by mast cells.

In response, applicants argued the ability of CPPs to successfully deliver a *specific* biological agent needs to be empirically determined. The applicants' own work and the published work of others clearly demonstrated that only the claimed CPP inhibits mast cell secretion. The other three CPPs do not work. Two Rule 132 declarations were submitted to support this conclusion. By argument and declaration, applicants explained that the unpredictability of the two mast cell inhibitor peptides to inhibit mast cell

secretion once fused to a CPP arise from a variety of unpredictable factors. It was explained that once CPP penetration has occurred, the biological effect of the mast cell inhibitor cargo peptide on the mast cell can be influenced by: (i) conformation changes associated with the fusion; (ii) degradation of the "foreign" peptide in the cell; (iii) sequestering of the fusion peptide in an endosome; or, (iv) ability of the CPP to trigger mast cell release.

The Examiner expressly ignored the data and declarations. She argues that she is entitled to focus entirely on the teachings of Lin disclosing the Kaposis' CPP (AAVALLPAVLLALLAP) and ignore the negative results from the other three CPPs. In effect, she renders the *prima facie* case of obviousness irrebuttable. She writes on page 4 of the Final Office Action mailed on November 29, 2007:

> In this case, the data (that shows other CCP [CPP-sic] peptides fail to inhibit histamine secretion is inadequate evidence that the claimed CCP of SEQ ID NO:3 is unpredictable. Even if the field of CPP technology is unpredictable, the instant SEQ ID No.:3 has been consistently shown to be predictable in delivery of biological cargo peptides and maintaining the functions of said peptides (see Lin et al. and the Sagi-Eisenberg declaration and Razin declaration filed on June 28, 2007.

The Examiner's selective focus on the Lin disclosure of the Kaposi CPP arises from no objective rationale. The prior art does not favor or recommend the Lin CPP over the other CPPs. The two declarants state in ¶5 that prior to the applicants' work, all the CPPs were considered to be essentially equivalents. They both wrote:

> Because the prior art literature would suggest to those of skill that CPPS are interchangeable, it is surprising that the choice of CPP would be critical for obtaining biological activity.

In other words, no reference says that the Lin CPP is better than the other CPPs. It was the applicants' experimental work that determined this—at least for the two mast cell inhibitors recited in the rejected claims.

The applicants' evidence presents a classic fact pattern for traversing a *prima facie* case of obviousness. Unlike the recent, *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 (Fed.

Cir. 2007), this is not a situation of someone selecting the *best* combination from a limited group of choices (salts) all of which were known to work to some degree. Here the other choices (CPPs) don't work. According to the literature, any CPP should have worked; but, three of the four did not work with the two inhibitors being claimed.

The pending claims are appropriately limited to the working embodiments. In the undersigned attorney's experience, an inventor could not have presented a stronger story for traversing a *prima facie* case of obviousness.

This rejection reflects a serious misunderstanding of the law relating to traversing a *prima facie* case of obviousness. An examiner cannot ignore the rebuttal argument and selectively focus on references that support his/her position. *Akzo N.V. v USITC*, 1 USPQ 2d 1241 at 1246 (CAFC 1986).

Applicants respectfully submit that the rejection is not legally proper and request reconsideration and withdrawal of this basis for rejection under §103. The other rejections are dependent upon this §103 rejection. If the reviewing panel agrees with the applicants' position, the claims should be in condition for allowance.

Respectfully submitted,

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